PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 31789	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL2005/000358	International filing date *(day/month/year)* 30.03.2005	Priority date *(day/month/year)* 30.03.2004
International Patent Classification (IPC) or national classification and IPC INV. C07K16/28 C07K16/42 A61K39/395 A61P37/08		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY ...		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.05.2006	25.08.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Covone-van Hees, M.G Telephone No. +31 70 340-4416

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2005/000358

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-55	as originally filed
Claims, Numbers	
1-19	filed with telefax on 15.05.2006
Drawings, Sheets	
1/21-21/21	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: Ott VL et al. (2000)
D2: WO03064662
D3: WO03030835

2. **Novelty** (Article 33(2) PCT)

1. The documents D1-D3 are regarded as being the closest prior art to the subject-matter of claims 1-19.
2. D1 reviews the coaggregation of inhibitory receptors (ITIM) e.g. FcγRIIB, gp49 and activating receptors (ITAM) e.g. FcεRI on mast cells as a possible therapeutic target for atopic diseases and allergies (see pg.430 left-hand column 3rd paragraph; "concluding remarks). Coaggregation of gp49 and FcεRI inhibits mast cells activation (see pg.434 right-hand column l.34-37). IL-5 contributes in recruiting eosinophils during allergic reactions (see pg.429 right-hand column l.12-14).
3. D2 studies the cross-linking of FcεRI (ITAM) and HM18 (mouse equivalent gp49) or FcγRII (ITIM) with bispecific antibodies to treat allergies (see pg.2 l.20 - pg.4 l.10; ex.2-4).
4. D3 teaches also the cross-linking of ITAM and ITIM to treat e.g. asthma. Several ITAM-ITIM combination are suggested (see pg.3 l.10-18; examples).

5. None of the available prior art documents however mention a bispecific antibody for targeting the ITAM IRp60. Consequently the subject-matter of claims 1-19 appears to be novel (Article 33(2) PCT).

3. **Inventive Step** (Article 33(3) PCT)

1. Document D1-D3, are considered to represent the most relevant state of the art, whereby all three documents (see point 2.2-2.4) discloses the concept of cross-linking activating and inhibitory receptors in order to inhibit mast cells activation. D1 moreover also identifies eosinophils to be involved in the allergic response.
2. The problem to be solved by the present invention may be regarded as providing a bispecific antibody targeting an alternative ITAM on target cells (mast cells, eosinophils or basophils).
3. The solution to this problem proposed in the claims of the present application is to target Irp60. Irp60 is a ITIM receptor which exerts its inhibitory function on mast cells, eosinophils and basophils by cross-linking in a homotypic mode, contrary to the receptors disclosed in D1, D2 or D3 which require cross-linking of activating and inhibitory receptors. A further unexpected advantage of the claimed antibodies consists in their specificity as they bind only to the target cells, while the known ITAM and ITIM receptors may bind NK cells. Therefore, the use of Irp60 to target mast cells, eosinophils and basophils in the claimed antibody is considered to involve an inventive step and claims 1-19 fulfill the requirements of Article 33(3) PCT.

4. For the assessment of the present claims 16-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.
2. Claim 2 recites "said cell" while the no reference exists in claim 1 for a cell.

3. The scope of claim 8 appears to be equivalent to the scope of claims 9-13.

Re Item VIII

Certain observations on the international application

1. The terms "homologues thereof" and "functional fragment" used in claims 1, 6 and 9-13 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT. Although such terms are commonly used in the art, their unclear meaning casts doubts to the exact scope of the claims.

Claims:

1. A bi-specific antibody or any functional fragment thereof comprising:

(i) a, first target recognition component which specifically binds to the inhibitory receptor IRp60 or homologues thereof; and

(ii) a second target recognition component which specifically binds to a marker specific for a mast cell, an eosinophil and/or a basophil.

2. The bi-specific antibody of claim 1, wherein a binding of said antibody to said cell inhibits allergic-type reactions.

3. The bi-specific antibody of claim 1, wherein said first and second target recognition components are linked via any one of a cross-linker, a linker compound, a carrier, a synthetic spacer, an immobilizing substrate and a $(Gly_4Ser)_3$ motif based flexible region.

4. The bi-specific antibody of claim 1, wherein said first and second target recognition components are cross-linked.

5. The bi-specific antibody of claim 1 4, wherein said marker may be selected from the group consisting of immunoglobulins, Fc receptors, cytokine receptors, growth factor receptors, adhesion molecules, Ig-superfamily receptors, chemokine receptors, inflammatory mediator receptor, hormone receptors, complement factor receptors, protease-activated receptors and enzymes.

6. The bi-specific antibody of claim 1, wherein said recognition component is selected from any one of a naturally occurring, synthetic or recombinant antibody, single chain Fv (scFv), bi-functional scFv, diabody, F(ab) unit, F(ab') unit, bi-specific F(ab') conjugate, chemically cross-linked bi-functional antibody, linear antibody, F(ab')2 antigen binding fragment of an antibody, or any functional fragments thereof.

7. The bi-specific antibody of claim 1, wherein said recognition component is a F(ab') unit.

8. The bi-specific antibody of claim 1, wherein said marker is one of IgE, cKIT, IL-5R, CCR3 and FcεRI.

9. A bi-specific antibody or any functional fragment thereof comprising:

(i) a, first target recognition component which specifically binds to the inhibitory receptor IRp60 or homologues thereof; and

(ii) a second target recognition component which specifically binds IgE.

10. A bi-specific antibody or any functional fragment thereof comprising:

(i) a, first target recognition component which specifically binds to the inhibitory receptor IRp60 or homologues thereof; and

(ii) a second target recognition component which specifically binds c-KIT.

11. A bi-specific antibody or any functional fragment thereof comprising:

(i) a, first target recognition component which specifically binds to the inhibitory receptor IRp60 or homologues thereof; and

(ii) a second target recognition component which specifically binds FcεRI.

12. A bi-specific antibody or any functional fragment thereof comprising:

(i) a, first target recognition component which specifically binds to the inhibitory receptor IRp60 or homologues thereof; and

(ii) a second target recognition component which specifically binds CCR3.

13. A bi-specific antibody or any functional fragment thereof comprising:

(i) a, first target recognition component which specifically binds to the inhibitory receptor IRp60 or homologues thereof; and

(ii) a second target recognition component which specifically binds IL-5R.

14. A pharmaceutical composition comprising as active agent at least one of the bi-specific complex of any one of claims 1 to 13.

15. The pharmaceutical composition of any one of the preceding claims, further comprising buffers, additives, stabilizers, diluents and/or excipients.

16. Use of at least one of the bi-specific antibodies of any one of claims 1 to 13, in the preparation of a pharmaceutical composition for the treatment of any disease or condition associated with mast cell and/or eosinophil and/or basophil mediated reactions.

17. The use of claim 16, wherein said disease or condition is selected from the group consisting of: allergic asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis and atopic eczema, allergic disorders and responses to various allergens, systemic anaphylaxis, systemic mastocytosis, morphea/urticaria pigmentosa, mast cell leukemia, atherosclerosis, graft rejection, multiple sclerosis, fibrotic lung diseases, neurofibromatosis, keloids, scleroderma, rheumatoid arthritis, osteoarthritis, acute gout, ocular cicatricial pemphigoid, Crohn's disease, peritoneal adhesions, chronic graft versus host disease (GVHD), eosinophil myalgia syndrome, bronchial asthma, nasal

polyposis, Wegener's granulomatosis, interstitial and other pulmonary diseases, chronic eosinophilic pneumonia, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, sarcoidosis, idiopathic pulmonary fibrosis, neoplastic and myeloproliferative diseases, T cell lymphomas and Hodgkin's disease.

18. The use of claim 16, for use in the treatment of any disease or condition derived from eosinophil hyperactivity or hyperplasia.

19. The use of claim 16, wherein said conditions are selected from the group consisting of extrinsic bronchial asthma, allergic rhinitis, onchocercal dermatitis, atopic dermatitis, nasal polyposis, nodules, eosinophilia, rheumatism, dermatitis, and swelling (NERDS), vasculitic granulomatous diseases, temporal vasculitis, Churg-Strauss syndrome, polyarteritis, Wegener's granulomatosis, multiple sclerosis, graft rejection, bronchial asthma, interstitial and other pulmonary diseases, eosinophilic pleural effusions, transient pulmonary eosinophilic infiltrates (Löffler), histiocytosis, chronic eosinophilic pneumonia, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, idiopathic pulmonary fibrosis, topical eosinophilia, cat scratch disease, afebrile tuberculosis, chlamydial pneumonia at infancy, neoplastic and myeloproliferative diseases, bronchogenic carcinoma, hypereosinophilic syndrome, T cell lymphomas and Hodgkin's disease, Crohn's disease, vernal keratoconjunctivitis, juvenile inflamed conjunctivitis nevus, Kimura's disease, Gleich's disease.